

REMARKS

Claims 21-38, 40-46, 48-54, 56, 57 and 63-75 are pending. Claims 21, 22 and 28 have been amended, and claims 1-20, 25-27, 39, 43-45, 47, 55, 58-62 are cancelled. Support for amended claims 21, 22 and 38 appears at, e.g., page 3, paragraph 3. Support for new claims 68-74 appears, e.g., in cancelled claims 25-27, 43-45, Table I on page 6 of the specification; and page 7, Note 4 and page 8, ¶ 4 (where the detrimental effect of glycerol is indicated). No new matter is added.

Claims 21-38, 40-46, 48-54, 56, 57 and 63-66 remain rejected as unpatentable over U.S. Patent No. 5,858,410 ("Muller") and U.S. Patent No. 5,739,152 ("Andersson"). The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner maintains that the claims are unpatentable over Muller in view of Andersson, asserting that the combination of trehalose with water insoluble drug and phospholipid would have been obvious based on the two references. The Examiner asserts in the August 5, 2010 Advisory Action that the presence of trehalose in combination with a water insoluble drug and a phospholipid reads on the claimed invention, regardless of the function of each component.

To address these comments, claims 21, 22, and 38, from which depend the remaining claims subject to the rejection, are amended in this response to require that the thermoprotecting agent is present in an amount effective to restrict an increase in volume weighted mean diameter of said suspension during and after terminal stem sterilization. As Applicants have discussed in previous responses, a composition with these features is not taught or suggested by Muller or Anderson, either individually or in combination.

Newly added claims 67-75 are further distinguishable over the cited references. Claims 67, 69, and 71 specify that the recited polydroxy thermoprotecting agent is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, and mixtures thereof. Claims 68, 70, and 72 require that the phospholipid surface modifier is egg phospholipid, soy phospholipid, or Lipoid E80®. Claims 73-75 specify that the composition lacks glycerol.

The artisan would not rely on Muller and Andersson to make the invention of claims 67-75. Muller targets the problem of reducing proportions of particles in the micrometer range by preparing the particles using an ultrasonic probe, a ball mill or a pearl mill, and by using cavitation or shearing and impact forces with high amount of energy. (*See* Abstract.) In preparing the suspensions of microparticles, Muller experiments with several surfactants and stabilizers known in the art. In an attempt to stabilize the nanosuspensions, Muller experimented with varying the concentrations of Tween 80, and teaches adding Lecithin in combination with ethoxylated block copolymers, such as Tween 80 and Pluronic for stabilizing microparticles. (*See* col. 7, lines 24-25; examples 6-16.) For smaller particles prepared by cavitation the preparation parameters are provided in Example 15, which includes Lecithin and Glycerol in combination with Pluronic F68. (*See* col. 17, lines 36-47.) The recipe for particles prepared by jet stream includes Lecithin, Pluronic F68 and Glycerol. (*See* Example 14, col. 7, lines 20-25.), and the procedure for particles prepared by autoclaving includes Tween 80 and mannitol. (*See* Example 10, lines 30-32.)

Muller focuses on using Tween 80 but does not teach using Lecithin with trehalose as a recipe for autoclaving. In addition, Muller finds that 1% Tween 80 showed visible aggregates after autoclaving (*see* col. 16, lines 63-65), and that after autoclaving the number of particles greater than 5 μ m rose as a result of aggregates (*see* col. 15, lines 53-55).

Such particles are excluded by the present claims. In addition, the present invention solves the problem of particle size increase during steam sterilization by including trehalose. Unlike Muller, where autoclaving proved to generate aggregates of particles, the current claims require that autoclaving does not create particle aggregation.

Moreover, combining Lecithin and Tween 80 or Pluronic would result in different microparticles than those currently claimed because particle sizes after steam sterilization would be approximately 4-fold larger than desired. (*See* p. 8, ¶ 5, to page 9, ¶ 1 of the specification) In addition, according to the current invention, glycerol would render the particles highly unstable, which is contrary to the requirements of the invention. (*See* p. 7, ¶ 5.)

Andersson does not remedy the deficiencies in Muller with respect to claims 67-75. Andersson teaches a pharmaceutical emulsion for intravenous administration comprising glycerol (*see* Examples 1-11, col. 6-7). In contrast, the present inventors discovered that glycerol destabilizes particles (*see* above), and Andersson teaches autoclaving as an option for sterilizing the nitrogen purged bottles. (*See* col. 6, lines 29-31.) However, Andersson teaches that when emulsions were autoclaved, no significant changes in stability was observed, except that autoclaved emulsions had a drop in pH, which could be avoided with sodium hydroxide. (*See* col. 6, lines 63-66.)

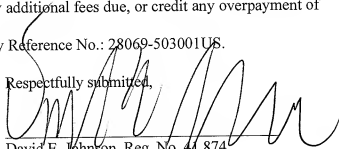
In not including trehalose as a thermoprotective agent, but including glycerol in an emulsion that is unaffected by autoclaving, Andersson does not describe or suggest the claimed invention. Without teaching any necessity for autoclaving the nitrogen purged bottles or for excluding glycerol, Andersson fails to remedy the deficiencies in Muller. One of ordinary skill in the art would not find any teaching, suggestion, or motivation in Andersson to combine with the disclosure in Muller to arrive at the instant invention because both Muller and Andersson teach

different inventions and when combined does not predict the result disclosed in the current application. Lacking any clear teaching, suggestion, or motivation in Andersson, the Examiner's finding of obviousness is hindsight reconstruction relying on the Applicant's invention.

Muller, alone or when combined with Andersson, does not therefore teach or suggest every element of the claims. Applicants request reconsideration and withdrawal of the rejection.

Applicants submit that the application is in condition for allowance and request an action for same. A petition for an extension of time and Request for Continued Examination accompany this response. Please charge any additional fees due, or credit any overpayment of same, to Deposit Account 50-0311, Attorney Reference No.: 28069-503001US.

Respectfully submitted,



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